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DIALYSIS – TRANSPLANTATION

Transplantation for primary hyperoxaluria in the United States

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Transplantation for primary hyperoxaluria in the United States.

Background. Transplantation (TX) has become an acceptable treatment for renal failure in primary hyperoxaluria (PH). We have analyzed data from three U.S. sources to estimate the success or failure of different modes of management in PH patients.

Methods. The United States Renal Data System (USRDS) tapes provided coded medical record data, with PH assigned to 235 patients from 1974 to 1996. Another 45 patients were found from USRDS hospitalization records. We limited patients to those developing end-stage renal disease at <55 years of age after 1984 (95 PH patients). The North American Pediatric Renal Transplantation Cooperative Study (NAPRTCS) identified 34 (11 new) PH patients, and the United Network for Organ Sharing (UNOS) database identified PH in 34 (16 new, 5 more in both UNOS and NAPRTCS) patients. These secondary sources were used to correct some data from the USRDS and to add 32 more patients, with a total of 128 PH patients. Considering kidney TX (KTX) prior to combined kidney/liver TX (K/LTX) as a separate record for some calculations, the total "cases" were 138.

Results. By life table analysis, the 94 total TX patient survival was better than for the 34 NoTX patients ($P < 0.001$). The 52 KTX patients' survival was better than either the 32 primary K/LTX ($P < 0.001$) or the 10 K/LTX that following KTX ($P < 0.001$). The 62 KTX cases' survival was better than the 42 K/LTX cases ($P < 0.005$), which did not differ from the 34 NoTX ($P < 0.67$). The overall survival of these 62 KTX patients was 76%. The survival of 42 K/LTX was 69%, and the survival of 34 NoTX patients was 44%. Kidney graft life table projected survival curves for TX patients did not differ between K/LTX (56% at 6 years) and isolated KTX (51% at 6 years, 35% at 10 years, $P < 0.91$).

Conclusion. KTX offers better patient survival in the United States then either K/LTX or NoTX. Graft survival does not differ between KTX and K/LTX. Because K/LTX can still follow a failed KTX, isolated living related donor KTX is still a reasonable first option for PH type 1 if a strictly managed protocol is followed.

Since 1984, our understanding of the pathogenesis and transplant management of primary hyperoxaluria (PH) patients has improved significantly [1]. In Europe, with poor results of isolated kidney transplantation (KTX), primarily from cadaveric donors performed before 1986, combined kidney-liver transplant (K/LTX) has predominated [2]. With referral to highly specialized centers common, the European consortium has systematically collected data on K/LTX [3].

To establish results in the United States without a central registry, we queried all of the available databases with more extensive data [4] and have combined that data to develop a comprehensive pattern. We show that TX for PH in the United States is a better option than NoTX because of the lesser risk of KTX. It appears that KTX currently remains a safer option than K/LTX for the patient with PH, recognizing that a meticulous protocol is necessary. K/LTX is still a surgical procedure with considerable risk for patient survival, although potentially curative. Although the proportion of patients receiving K/LTX has increased, the survival figures have not yet matched those of KTX.

METHODS

Data collection

Data from the United States Renal Data System (USRDS) was provided to the investigators as limited SAS transport data sets after application and permission from the USRDS scientific committee. Records dated from 1974 until 1996. The original source for the USRDS data was derived from Health Care Finances Administration (HCFA)-supported financial coverage of end-stage renal disease (ESRD). Privacy of all data was maintained, and identifying data were excluded throughout the study. Dates of transplant, sex, race, age, and region of transplant were used to exclude duplication and to match patients in the different databases. The USRDS data were considered comprehensive, likely including all patients with possible TX insurance coverage through Medicare or Medicaid. There was no check on diagnostic codes entered at the time of ESRD registration. These codes were not usually changed by USRDS when later information suggested a different diagnosis. Patients not

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covered by Medicare or Medicaid, such as primary liver transplant (LTX), foreign nationals, and independently funded patients, may not have been included.

The ICD-9 diagnostic code for hyperoxaluria (ICD9-2718) was assigned to 235 patients in the USRDS from 1974 to 1996. Using hospitalization records and transplant follow-up files to examine discharge diagnostic codes and surgical procedure codes, another 45 PH patients were found. The high mean age of the 280 patients (44.4 ± 23.4 SD years) was considered unlikely for PH. This suggested a questionable diagnosis in older patients, possibly secondary oxalosis caused by long-term dialysis therapy. For this reason, we arbitrarily excluded patients entering ESRD after the age of 55 years and those before 1984, when our aggressive approach was reported [1]. A few more were excluded whose data would have clearly excluded PH (that is, multiple hospitalizations for diabetes mellitus and systemic lupus erythematosis). By searching the USRDS surgical procedures and hospitalization discharge codes, 12 transplanted patients who had also received a liver transplant were identified.

Coded data were obtained from the United Network for Organ Sharing (UNOS), the organization that distributes primarily cadaveric organs for TX. Only the K/LTX data included appropriate diagnostic codes, including 34 transplants for PH, and were available for the years 1984 through 1996. It was felt that the diagnostic codes were relatively reliable, and because most U.S. K/LTX organs are supplied by UNOS, the codes were relatively inclusive. However, because follow-up in the UNOS system is not mandatory, outcome data may be less reliable.

Information was also obtained from the North American Pediatric Renal Transplantation Cooperative Study (NAPRTCS) as to which centers had PH patients coded. Each center was contacted, and we contacted those giving specific permission for detailed data about 34 PH patients with KTX and K/LTX and their course. The NAPRTCS database is voluntary, and thus, it may not be completely inclusive, even within those centers providing information. The personal communication assured that those included had relatively correct follow-up information.

The UNOS and NAPRTCS data were used to search the USRDS database, to add patients not previously identified in the USRDS as having PH, and to correct some data in the USRDS files. The final number of patients for analysis was 128. Considering the course of patients with KTX prior to K/LTX as separate KTX records for some calculations, the total number of "cases" was 138 USRDS patients, 62 of whom received KTX, 42 who received K/LTX, and 34 who received NoTX. When patients who ultimately received TX were considered NoTX for the period between ESRD and TX, there were 128 NoTX and a total of 232 cases (Table 1).

Data analysis

Transport data sets were imported into SAS, a statistical package from SAS Institute (Cary, NC, USA), and analyses were performed on subsets of this data using SAS version 6.08 on a DEC/VAX 6000-620 mainframe computer and version 6.11 on a IBM RS 6000 mainframe computer. Graphic processing used SigmaPlot 4.0 for Windows (Jahndel).

Life table analysis. The frequency and life table statistical procedures were performed using the actuarial approach [5]. Differences between two or more groups were analyzed by log-rank [6] and Wilcoxon test [7]. Log-rank data better reflected the earlier time periods, when greater patient numbers were available. P values of less than 0.05 were considered significant.

RESULTS

Of the 95 patients from the USRDS limited to less than 55 years of age and entering ESRD since 1984, the age was now 30 ± 17 years (Table 2). Sixty-one had transplants (age 25.84 ± 16), and 34 had NoTX (age 39 ± 13 years, $P < 0.001$). One hundred and twenty-eight PH patients were analyzed in the database expanded by the UNOS and NAPRTC data. The age was 39 ± 12 years for the 34 nontransplanted patients and 22 ± 16 years for the 94 in the TX group ($P < 0.0001$; Fig. 1). NoTX primarily occurred in patients older than 20 (30 out of 34 patients), and K/LTX primarily occurred in patients younger than 20 years (32 out of 42 patients). KTX patients were more evenly distributed.

Life table analysis of patient survival in the TX and NoTX groups showed a marked and persistent difference at all time periods. Projected survival of the NoTX group, by life table analysis (40% at five years and 20% at nine years) differed from the transplanted group, which was 89% at five years and 63% at nine years ($P < 0.0001$ by both log-rank and Wilcoxon analyses).

Considering KTX preceding combined kidney-liver transplant (K/LTX) as a separate "case," the curve of the 62 KTX patients' survival was better (84% at 6 years and 55% at 9 years) than that of the 42 K/LTX (55% at 6 years and 40% at 9 years, with only one patient remaining between these years, $P < 0.005$; Fig. 2). This projected K/LTX patient survival curve was not different from the NoTX group ($P < 0.67$ by log-rank and $P < 0.72$ by Wilcoxon analysis). When patients who later received a TX are considered NoTX before that time, there are 128 cases in which the age is 25.64 ± 17.5, not differing from the KTX group ($P < 0.44$), although the survival curve still differs. The LTX group is significantly younger (14.31 ± 14) than the NoTX group, but the survival curve does not differ ($P < 0.67$).

To obtain age-comparable groups, patients (not cases) can be separated at 20 years. For more than 20 years,

Table 1. Summary of all database groups

Transplant group	KTX	K/LTX			NoTX	Total
		Primary	Secondary	Total		
USRDS Dx = PH	96	X	X	X	139	235
USRDS Dx = Px plus others	124	X	X	X	156	280
USRDS total < 55 years, after 1984	44			17	34	95
UNOS total K/LTX for PH	0	27	7	34		34
NAPRTCS total PH	16	10	8	18	0	34
PH only in UNOS	0	16	0	16	0	16
PH only in NAPRTCS	8	3	0	3	0	11
PH in both UNOS & NAPRTCS	0	4	1	5	0	5
All PH patients, <55 years, after 1984	52	32	10	42	34	128
All PH cases, <55 years, after 1984	62	32	10	42	34	138
All cases plus NoTX pre-Tx	62	32	10	42	128	232

Abbreviations are: Tx, transplant; K, kidney; L, liver; USRDS, United States Renal Data System; Dx, ?; PH, primary hyperoxaluria; UNOS, United Network for Organ Sharing; NAPRTCS, North American Pediatric Renal Transplantation Cooperative Study.

Table 2. Results of three databases, for patients <55 years, diagnosed after 1984

Transplant group	KTX	K/LTX			NoTX	Total
		Primary	Secondary	Total		
All PH cases, <55 years, >1984	62	32	10	42	34	138
Lifetable survival @ 6 years	84%	65%	43%	56%	50%	
Total # surviving	47	25	5	29	15	91
Total # dying	15	7	5	13	19	47
Final % surviving	0.76	0.78	0.50	0.69	0.44	0.66
Lifetable graft survival @ 6 years	50%	65%	43%	56%		104
Total grafts surviving	30	25	5	29		59
Grafts failing	32	7	5	13		45
Final % surviving	0.48	0.78	0.50	0.69		0.57
All cases plus NoTx pre-Tx	62	32	10	42	128	232
Lifetable survival @ 6 years	84%	65%	43%	56%	50%	
Total # surviving	47	25	5	29		
Total # dying	15	7	5	13		
Final % surviving	0.76	0.78	0.50	0.69		

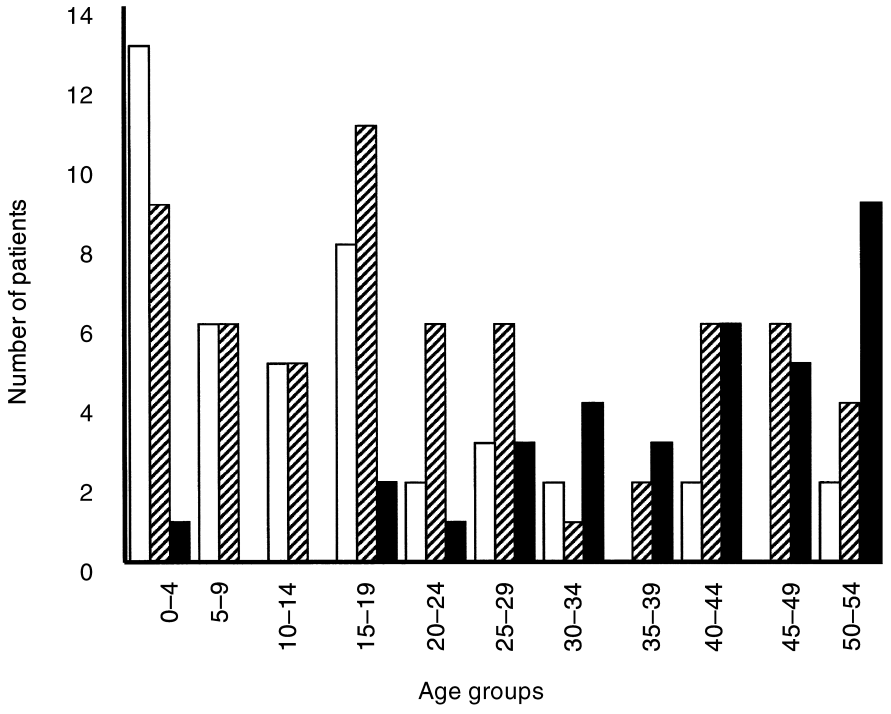

Fig. 1. Age distribution in primary hyperoxaluria (PH) patients from USRDS, NAPRTCS, and UNOS databases from 1986 through 1996, differentiating kidney transplant (KTX; ▨), kidney/liver transplant (K/LTX; □), and no transplant (NoTX; ■) groups of patients. The predominance of younger ages is seen in transplant patients, particularly K/LTX patients, in contrast to the nontransplanted group ($P < 0.001$).

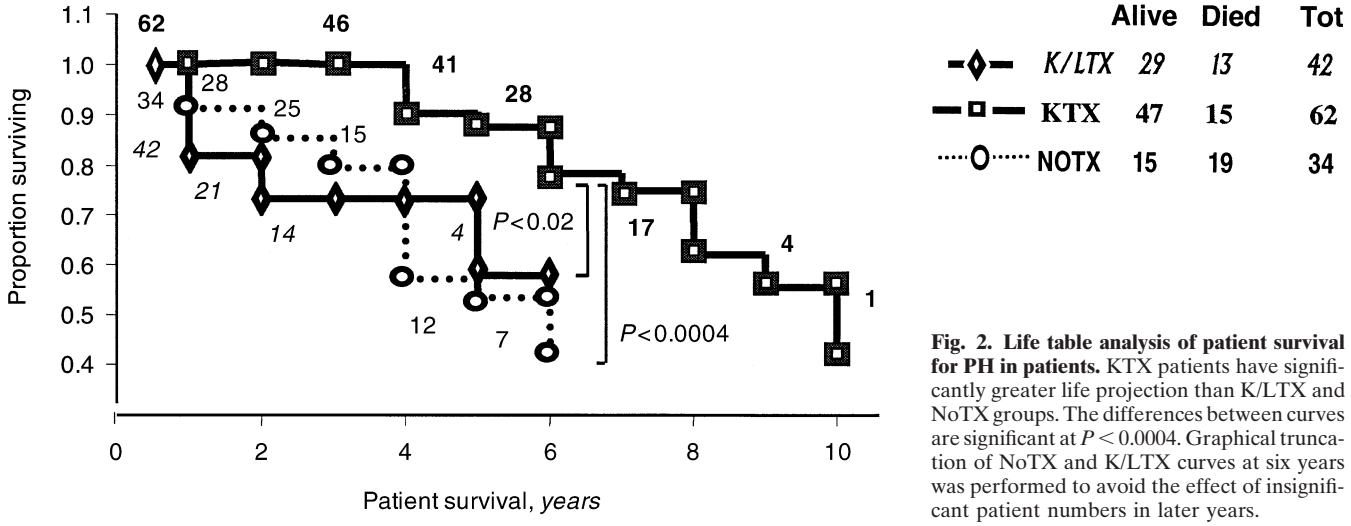

Fig. 2. Life table analysis of patient survival for PH in patients. KTX patients have significantly greater life projection than K/LTX and NoTX groups. The differences between curves are significant at $P < 0.0004$. Graphical truncation of NoTX and K/LTX curves at six years was performed to avoid the effect of insignificant patient numbers in later years.

KTX patients' ages are similar to NoTX patients (37.57 ± 11.05 vs. 42.2 ± 9.64 year, $P < 0.08$), but life table survival curves differ significantly ($P < 0.0001$). Likewise, the ages of K/LTX patients of less than 20 years (7.9 ± 6 years) do not differ from KTX patients of less than 20 years (9.6 ± 7, $P < 0.32$), but the survival curves still differ significantly ($P < 0.03$).

The cumulative survival figures over the entire time period of the study showed that 46 of 62 KTX patients (74%), 29 of 42 KLTX patients (69%), and 15 of 34 NoTX patients (44%) survived. The small numbers of KLTX patients with greater than six years of follow-up explain the significantly differing curves with similar projected final numbers.

The comparison of the UNOS K/LTX PH patients with the total group of K/LTX patients showed that the (34) PH patients had a five-year 60% life table survival, virtually the same as that of the 282 non-PH K/LTX patients.

First, transplant KTX patient survival for 29 USRDS patients had been analyzed in 1994 [8]. At that time, it appeared that living-related transplant might result in better patient survival than cadaver transplant ($P = 0.058$). Updated data on these same patients showed a convergence of curves ($P < 0.97$). The number of patients receiving cadaver KTX in the NAPRTCS database, in which certainty of outcome data is more likely, was too few for analysis.

Specific data on kidney survival was not available for K/LTX patients. Because in the patient with K/LTX we have given K/LTX the benefit of assuming kidney graft survival if the patient survives, we used patient survival for K/LTX compared with kidney graft survival for KTX. By these criteria, kidney graft survival curves did not differ between K/LTX (56% at 6 years) and isolated KTX (44% at 6 years and 33% at nine years, $P < 0.91$; Fig. 3).

In PH patients, the duration of dialysis for ESRD prior to TX was 1.12 ± 1.1 years. (KTX 1.01 ± 0.9, all K/LTX patients 1.79 ± 2.0 years, primary K/LTX 1.05 ± 0.7 years, $P < 0.43$). There was no demonstrable difference for duration of dialysis between TX patients who died (1.31 ± 1.28, median 0.58) and those who were alive (1.05 ± 1.04, median 0.88) before KTX or K/LTX ($P < 0.95$).

DISCUSSION

This is the first comprehensive review of TX in PH patients in the United States, to our knowledge. From the data obtained, it is apparent that so far, after the onset of renal failure, belonging to the renal TX group offers a far better chance of projected patient survival in PH than belonging to the NoTX group. A causative relationship cannot be implied, only an association. Selection bias could be responsible. Difference in ages between the TX and NoTX groups could reflect such a selection bias, although the expansion of the database by including the pre-TX period as NoTX makes the ages of KTX and NoTX patients similar, but life table curves still differ. Furthermore, dividing patients at ages of less than 20 years from those with more than 20 years allows a comparison between KTX and K/LTX, in which ages are similar but life table survival for KTX is still greater than K/LTX ($P < 0.03$). Selection bias could also result from diagnostic error, mistaking secondary oxalosis in the older patient for PH. We have therefore truncated the entire database at age 55 and examined the hospitalization records of the USRDS patients for inconsistencies.

There is little support in the literature for isolated cadaveric kidney transplant for PH. However, from these

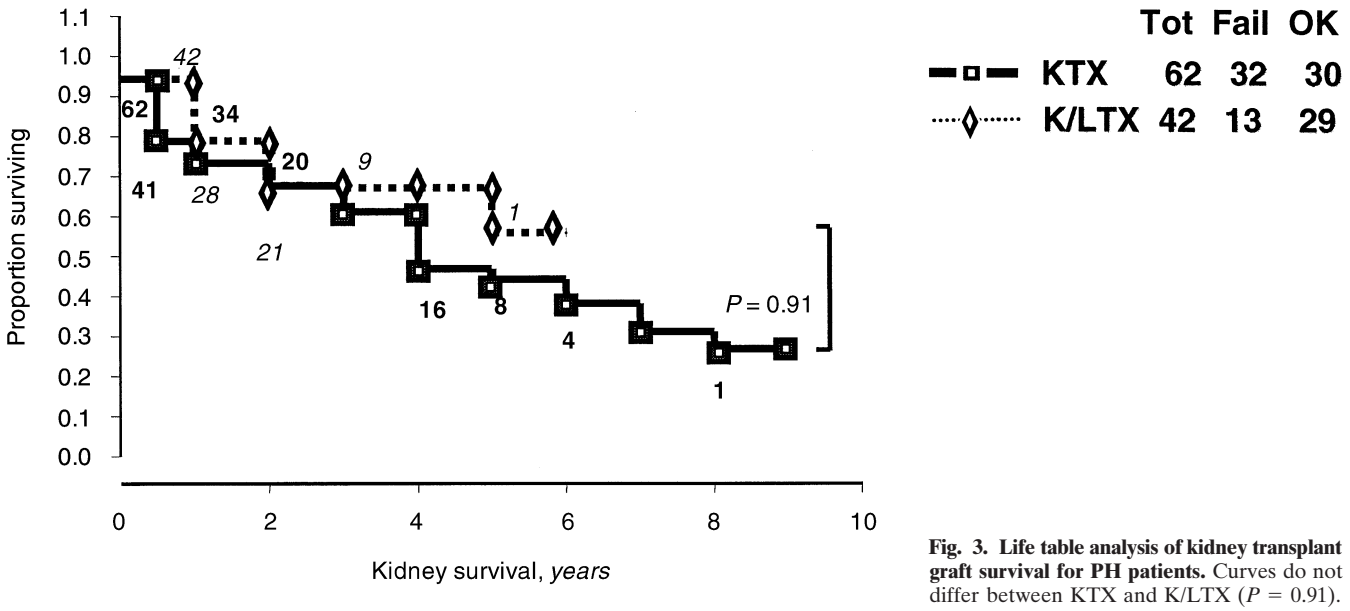

Fig. 3. Life table analysis of kidney transplant graft survival for PH patients. Curves do not differ between KTX and K/LTX ($P = 0.91$).

data, statistical analysis does not demonstrate different patient life survival for cadaver than live-donor kidney transplant. Because of the fewer cadaveric transplants, the life table curves of graft survival could not be shown to differ. In the direct experience of the authors and contacts with other centers, it appears that successful cadaver transplant for PH remains quite rare. Isolated kidney transplant for PH still appears to have reasonable success in this pooled series, 50% graft survival at five years, as in our previous reports, when a strict protocol is followed [9, 10]. Note that the NAPRTCS data on non-PH pediatric long-term patient (94% at five years in LRD) and graft (73% in LRD) survival for renal TX shows patterns similar to those observed for PH patients (87% at five years for patient survival and 51% at six years for all grafts). The rate of long-term graft success in PH has been found independent of the activity levels of alanine-glyoxylate-amino-transferase AGT [11].

Kidney/LTX for the PH patient with ESRD is attractive and potentially curative. Although clinical details are not available, K/LTX is still a hazardous venture in the United States, no matter if it is performed in the first instance or following a failed kidney transplant. The considerable risk of combined kidney-liver transplant for PH patients in the United States requires special attention to the indications for the procedure [10]. Because plasma oxalate determination is not widely available in the United States but may be necessary to rule out vitamin B6 response, in many cases it is not clear that a K/LTX "cure" is actually necessary. K/LTX is unreasonable without excluding the B6 response, by oxalate and/or glycolate assay [12], relative to plasma creatinine in the ESRD patient. While a consensus definition of the B6-response has not been finalized, it was an issue recently addressed by the Fifth International Workshop on Primary Oxaluria (March 12–13, 1999, Zurich, Switzerland). Normalization or a sustained 50% decrease in urine oxalate excretion or in the plasma oxalate/creatinine or glyoxalate/creatinine ratio (thus correcting for renal function) [14], after two to three weeks of large (>500 mg/1.73 m^2) daily doses of B6, will imply a B6 response, making liver replacement unnecessary.

The European approach is directed to K/LTX almost exclusively [13], and recent results support its continuation [3]. The European data on isolated renal TX in PH were derived before the modern era [2], showing a three-year graft survival of 23% in living related donors (LRDs) and 17% in cadaveric grafts following conventional transplant protocol. The causes of graft loss in the majority of the cases were rejection (33%) and recurrence of the primary renal disease (31%). A general update of data in children was performed in 1993 [14], showing a five-year graft survival of 38% of 9 LRDs and 26% of 37 cadaveric grafts in PH patients transplanted after 1985, which contrasts with the 71% graft survival for transplants performed in 1986 for the total pediatric population in the EDTA-ERA registry. No updates of the data have been made to this date. Factors including predominance of cadaveric transplant in Europe and the absence of an appropriate protocol for PH in earlier years may explain the differences between Europe and USA in terms of renal TX for PH [15].

The recent results of the European experience for K/LTX for PH (1984 to 1997) [3] showed a two- and five-year patient survival of 80 and 72%, respectively, and a renal graft survival of 78 and 62% at the same time

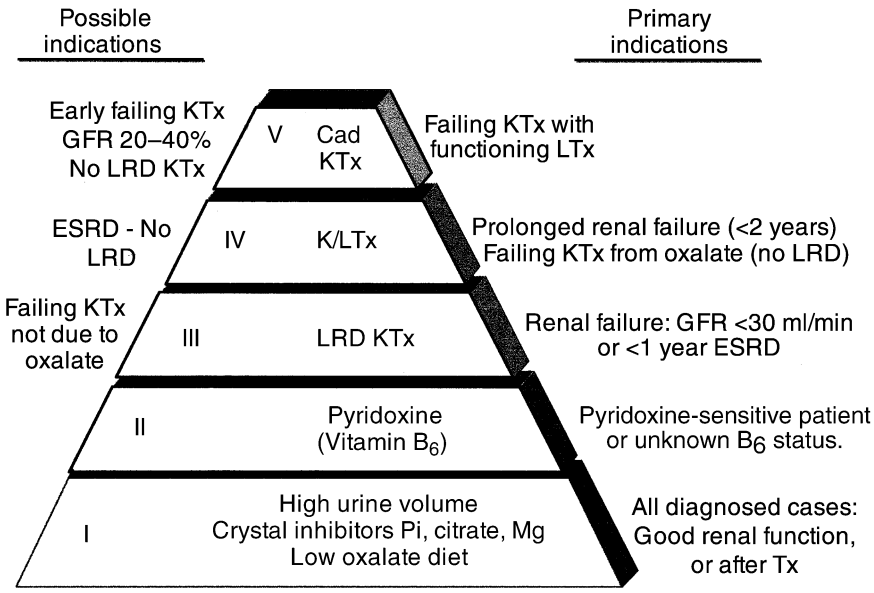

Fig. 4. Treatment choices for PH (adapted with permission from *Pediatric Transplantation* 1:4–7, 1997).

points. Note that this is approximately the same graft survival that we derived for primary K/LTX patients in the United States. At six years, our analysis of the U.S. experience showed a two- and five-year K/LTX patient survival of 79 and 55%, respectively, and an isolated kidney graft survival of 55% at five years. If indeed the life table curves differ between this and the European series, the reasons for apparently better patient survival in the European series are not known, as the specific causes of death in our series are not clarified, nor are the conditions of the patients at the time of transplant. The cumulative mortality of European K/LTX patients after 10 years was 23%, and for our U.S. series, it was 31%.

Jamieson felt that the time of dialysis and clinical condition of the patient were risk factors for the patient's survival in the European series [3]. However, the use of a classification of the degrees of severity of the patient conditions was subjective, and inferential statistical analysis to compare the survival curves was not performed. We were unable to show with our data that the time on dialysis prior to KTX or K/LTX was a significant factor in the TX patient's survival, in spite of such a clinical impression.

In summary, transplant represents a good option for ESRD patients with PH. The use of cadaver kidney transplant in patients with PH should be restricted to selected cases, probably those with slowly failing prior KTX or aggressively dialyzed patients when the vitamin B6 response is present [15]. K/LTX, while potentially curative, still carries with it a considerable risk for patient survival. The K/LTX procedure can still follow a failed KTX but requires testing for B6 sensitivity. KTX is a reasonable option if a strictly managed protocol is followed and a LRD KTX is available.

Until a more cooperative effort is made in the United States that decreases patient mortality, special considerations should be made to clarify the specific indications for K/LTX in the management of the disease (Fig. 4). Our suggestion is that in the United States, K/LTX should be performed in those PH patients who have no response to B6, prolonged renal failure (more than 2 years), a failing KTX from oxalosis (with no LRD kidney available), and in those PH patients initially developing ESRD who have no KTX donor available. In this sense, special efforts are necessary to improve universal pyridoxine response testing in the patients and meticulous monitoring of the oxalate levels in the transplant.

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